Metabolic Liver Disease

Introduction

In this lesson, we focus on the diseases that affect hepatocytes directly. We start with how to interpret liver function tests (LFTs) and fulminant hepatic failure. We then transition into the chronic metabolic liver diseases that, if untreated, will result in cirrhosis.

We cover Wilson's disease, primary hemochromatosis, α-1 antitrypsin deficiency, non-alcoholic fatty liver disease, and alcohol-related liver diseases—both acute alcoholic hepatitis and chronic progression to cirrhosis. "Alcoholic" is the adjective meaning "due to alcohol," and not a characteristic of the person who has cirrhosis. Alcoholic cirrhosis can occur in patients who do not have the disease of addiction, but alcoholic cirrhosis does require excessive alcohol consumption to occur.

Labs of Hepatocellular Dysfunction

There are three main categories of liver function: hepatocyte integrity, biliary excretory function, and hepatocyte synthetic function. When engaged in clinical work, you will want a shorthand way of writing things down. We introduce the OnlineMedEd LFT tree (which is different from that of most places, but the same as Tulane and UCSF Internal Medicine's) and show you how its orientation is deliberate to facilitate the assessment of liver injury.

Hepatocyte integrity. The cytosolic hepatocellular enzymes are aspartate aminotransferase (**AST**) and alanine aminotransferase (**ALT**). They are placed next to each other in the LFT tree because they are both enzymatic evidence of Acute liver disease (AST and ALT). Usually, ALT is elevated more than AST. When the AST:ALT ratio exceeds 2:1, suspect alcoholic liver disease or cirrhosis.

Hepatic biliary excretory function. The enzymes on the surface of the bile canaliculi and cholangiocytes are alkaline phosphate (**ALP**) and gamma-glutamyl transpeptidase (GGT). ALP is made in both the bone and biliary tree. LFTs report ALP but do not routinely report GGT. It is in the lowest position on the tree because it has no comparative enzyme. It is listed in green because it is a biliary enzyme. The substances the hepatocytes dump into the biliary tree are bilirubin, bile acids, and cholesterol. The LFTs always report **total bilirubin** (T. bili), although you often must specifically order **direct bilirubin** (D. bili). The T. bili is in red because it could be due to any cause, hemolytic to obstruction, so it is left in the prehepatic position by color. The D. bili is in green because it is a marker of biliary dysfunction. It is next to the T. bili so that a rapid calculation can be made to determine unconjugated bilirubin (indirect) by subtracting direct from total.

Hepatocyte synthetic function gets complicated quickly, so we try to simplify it. The liver synthesizes albumin and clotting factors. Total protein is listed in the upper left of the tree to compare with albumin, top right. The difference between the total protein and albumin should be < 4. If there are more non-albumin proteins, they usually come in the form of immunoglobulins, and a **protein gap > 4** is indicative of HIV, Hep C, multiple myeloma, or sepsis. The total protein and albumin are next to each other to enable a rapid calculation of the protein gap, subtracting albumin from total protein. The albumin is on the top of the LFT tree so that the three-pointed Mercedes-Benz sign can be placed on top, making a nice little house with total protein, albumin, and the **INR**, the standard way of monitoring for alterations in clotting factors. The Mercedes-Benz sign is the coagulation labs, which include PT and PTT (in their abbreviated forms only until Heme/Onc). The combination of albumin and the INR gives a rapid look at synthetic function, or **chronic liver labs** (as opposed to those of hepatocyte integrity, which are acute liver labs).

Other labs help with synthetic function—ammonia, platelets, blood count. The MELD criteria are used to score a cirrhotic liver, an objective evaluation of how in need a patient is of a transplant. The MELD is calculated using bilirubin, sodium, creatinine, and the INR. The LFTs and coagulation panel take you a long way. Figure 4.1 shows the different patterns of liver injury, as well.

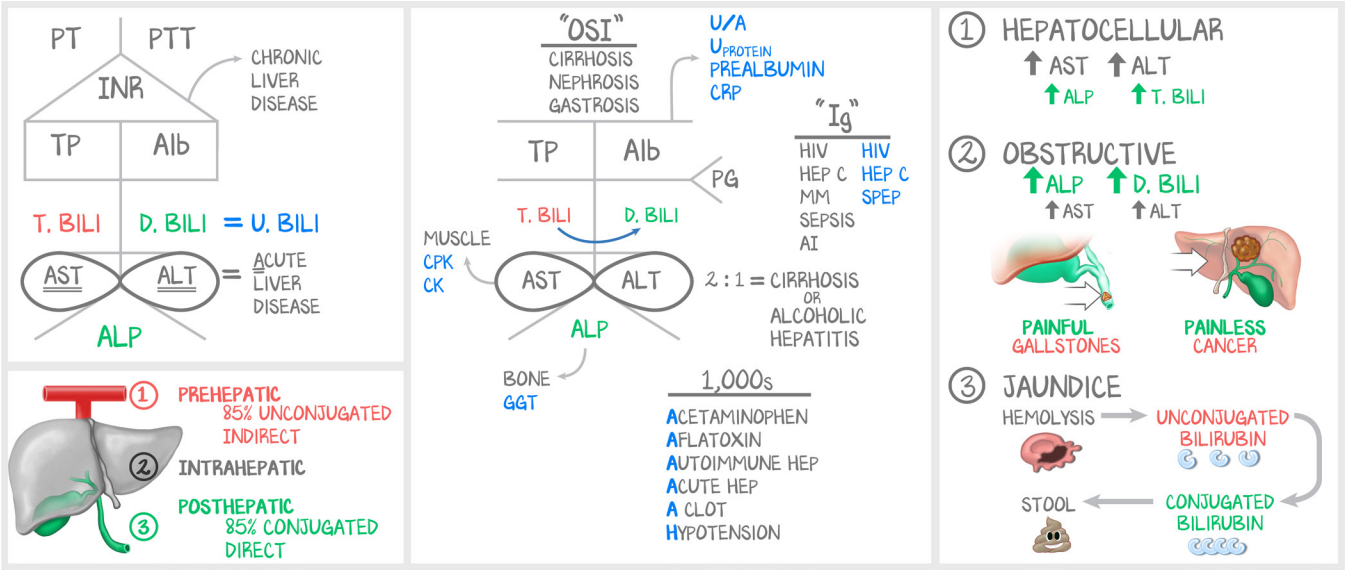

Figure 4.1: Liver Function Tests
This is a very advanced method for utilizing liver function tests—labs alone—to home in on the most likely diagnosis. The LFT sticks (the tree) combined with the coagulation Mercedes-Benz (INR on the bottom) enables the provider to see chronic liver function (INR, TP, Alb) separated from acute liver function (AST, ALT), and then color-code in prehepatic (red), posthepatic (green), and intrahepatic (grey). Everything blue is indicative of the reflexive test (no clinical reasoning, but a good move for an overnight call) that should be thought of when an abnormality is found. This won't make sense to you if you've never filled in the LFT sticks or the INR Mercedes-Benz, but this is a glimpse into the clinical world of liver disease.

Acute Liver Failure

Very few things can do sufficient hepatocellular damage to get the AST and ALT in the thousands. Those are remembered by the "6 A's": Acetaminophen, Aflatoxin (mushrooms), Acute viral hepatitis (A, B, and E), Autoimmune hepatitis, A clot (Budd-Chiari), and Hypotension (not an "A," but if you have bad handwriting it might be hard to tell). The AST and ALT being in the thousands is an impressive thing to see—they are normally < 50.

If there is evidence of fulminant hepatic failure, the etiology should always be pursued, and all "six A's" investigated.

The degree of AST and ALT elevation IS a sign of the severity of hepatocyte necrosis. The degree of AST and ALT elevation is **NOT** a determinant of fulminant hepatic failure. **Fulminant hepatic failure** is defined by the **loss of synthetic function** of the liver as measured by **hepatic encephalopathy** and the **INR**. If the INR is greater than 1.5, and the patient has hepatic encephalopathy of any severity and **no history of liver disease**, the patient is in fulminant hepatic failure.

If the patient goes into fulminant hepatic failure, their mortality, without transplantation, approaches 100%. This is a clinical diagnosis and is most appropriate for the clinical years. You likely won't be asked to identify or manage fulminant hepatic failure. We start this lesson off with a clinical discussion of LFTs and fulminant hepatic failure to put the diseases we are about to discuss into context.

Metabolic Liver Diseases

The diseases that follow are chronic diseases of the liver. They all inevitably lead to cirrhosis if untreated and unaddressed. We do not teach them in the order of the OME mnemonic from the Clinical Sciences here in the Basic Sciences, where we focus on the mechanism of hepatocellular injury and the histological appearance of the cells. We covered the autoimmune cholangiopathies—which can lead to cirrhosis—in the last lesson. They lead to the phenotype of cirrhosis known as biliary cirrhosis. The diseases in this lesson generally all result in the typical nodular cirrhosis common to alcoholic cirrhosis and chronic viral conditions. We introduce Dr. Williams' advanced organizer used in the Clinical Sciences, "VW-HAPPENS," now, and use it as a framework for the lesson. The video lesson goes in a different order than the notes because he follows the organizer. We start with the most prevalent cause of cirrhosis in the United States—alcohol—then progress in order of the causes not taught elsewhere (viral in Microbiology, PBC and PSC in the last lesson).

VW-HAPPENS stands for **V**iral hepatitis (B and C), **W**ilson's, **H**emochromatosis, **A**ntitrypsin deficiency, **P**rimary sclerosing cholangitis, **P**rimary biliary cirrhosis, **E**tOH, **N**AFLD, and **S**omething else.

Alcoholic Liver Disease

There are three distinct histological stages of alcoholic liver disease: steatosis, steatohepatitis, and steatofibrosis. You will notice that all three have fat in them—steato. The histological progression of alcoholic liver disease always involves lipid-laden hepatocytes. Alcohol is detoxified in zone 3. The steato, hepatitis, and fibrosis are found in **pericentral hepatocytes** (zone 3) in alcoholic liver disease.

Steatosis is the accumulation of fat droplets in hepatocytes. Steatosis occurs in small amounts with the ingestion of any alcohol—the more that is consumed, the more fat that accumulates. The longer alcohol is drunk, the more fat that accumulates. If alcohol use ceases, the fat accumulation will resolve. Alcohol (and other drugs) are processed in zone 3. Fatty acid synthesis is in zone 3. It is logical then, that fat would accumulate in hepatocytes in that zone. Fatty acid synthesis is regulated in part by the macro-control exerted by the pancreas (insulin means make more fat, glucagon means burn it), but it is also regulated by the availability of cytoplasmic substrate. Alcohol dehydrogenase and aldehyde dehydrogenase **consume NAD+** and **generate NADH**. In the hepatocytes that manage lipid synthesis, the presence of NADH stimulates fatty acid synthesis, thereby regenerating NAD+. Alcohol also causes impairment of the assembly and secretion of lipoproteins, resulting in the **fat that is made staying in the hepatocyte**. Thus pericentral fat accumulation is a sign of alcohol consumption.

Steatohepatitis is the histological description of the diagnosis of **alcoholic hepatitis**. It is inflammation of the liver (hepatitis). It is acute (neutrophils). It is caused by alcohol (alcoholic). **Acute alcoholic hepatitis** is an acute illness that presents with AST and ALT elevations (with an AST:ALT ratio > 2:1 being suggestive of alcohol-induced injury), jaundice, and right upper quadrant pain. On histology, there are **neutrophils**. Alcoholic hepatitis is characterized by Mallory-Denk Bodies, balloon degeneration, and steatosis of hepatocytes, as shown in the images. The steatosis is there due to the chronic alcohol. The inflammation (histologically, neutrophils) is there from the acute event, the hepatitis. Alcoholic hepatitis tends to occur with increased consumption from baseline but does not necessarily require it. Several factors likely play a role. **Acetaldehyde** (ethanol's primary metabolite) is a toxin that induces lipid peroxidation and protein adduct formation, disrupting cytoskeletal and membrane function. Cytochrome P450 produces **reactive oxygen species** that damage membranes and proteins. Alcohol **decreases glutathione levels**, increasing sensitivity to those oxygen species. One bout of hepatitis can be fatal (20% mortality). Repeated bouts of acute alcoholic hepatitis accelerate fibrosis.

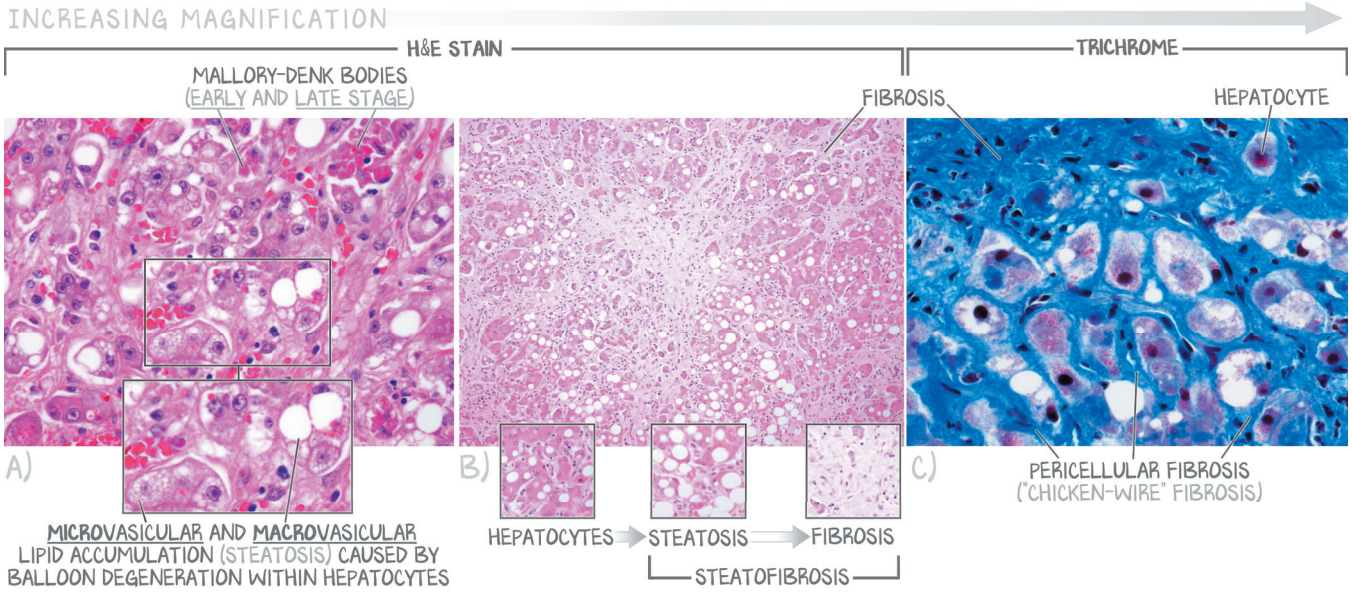

Figure 4.2: Histological Alcoholic Liver Disease

Steatofibrosis is the progression into early cirrhosis. There is both the **steato** (lipid-laden hepatocytes of steatosis from chronic alcohol) and **fibrosis** (a collagenous scar from neutrophils, macrophages, fibroblasts). This is the chronic form of hepatitis. Where neutrophils go, macrophages follow to clear the way and summon fibroblasts to scar down the "wound." The inflammation of acute hepatitis results in the release of cytokines that transform the stellate (Ito) cells into myofibroblasts. Even without ever having alcoholic hepatitis, ongoing damage from alcohol can result in fibrosis, although a history of alcoholic hepatitis significantly increases the risk and speed of development. Only 15% of patients with chronic alcoholism develop cirrhosis, implying that some initial inflammatory insult (like alcoholic hepatitis or concurrent viral hepatitis) is required for it to progress to fibrosis. Ongoing steatofibrosis is on a continuous spectrum with cirrhosis, the stages of which we talk about in GI: Hepatobiliary #5: *Cirrhosis*.

Wilson's Disease, Copper Metabolism

Wilson's disease is a disease of copper overload. The genetic defect in Wilson's disease is in the gene *ATP7B*. That gene codes for a membrane protein that is an ATPase, and its form is 7B. In normal copper metabolism, ATP7B is a transmembrane protein in a membrane-bound organelle (either the Golgi or a vesicle). It is the copper-transporting protein that gets the copper from the cytoplasm to within the membrane-bound organelle.

In times of low cytoplasmic copper, it remains a trans-Golgi protein, pumping copper into the Golgi, where copper finds **apoceruloplasmin** (apo-cerulo-plasmin). The apoceruloplasmin-copper complex, **ceruloplasmin**, is how the liver distributes copper to the rest of the body. Copper fills up all the seats on ceruloplasmin, then the Golgi buds off a vesicle with copper-rich ceruloplasmin to fuse with the sinusoidal domain of the hepatocyte, releasing ceruloplasmin into the portal system and sending it off to the body through the hepatic vein.

In times of high cytoplasmic copper, the trans-Golgi buds off a vesicle that still has ATP7B in the membrane, but has some non-apoceruloplasmin copper-binding proteins instead of apoceruloplasmin. ATP7B pumps copper into the vesicle, just as it would have into the Golgi where apoceruloplasmin was waiting. But instead of budding a vesicle to the sinusoidal membrane, this vesicle is already destined for the bile canaliculus, where it fuses and exocytoses the copper-protein combination into the bile. That copper-protein combination cannot be absorbed by enterocytes.

The sinusoidal transport protein (from the portal blood into hepatocytes) and the metallochaperone (cytoplasmic copper chaperone) are known but are not part of the pathogenesis of Wilson's, so we have purposefully excluded them. You are going to see a challenge question where they are included, but as we strictly emphasize in the text, **Wilson's is a defect of ATP7B** (both the gene *ATP7B* and the protein ATP7B).

In Wilson's disease, an **autosomal recessive** mutation in *ATP7B* causes a loss of function of the transmembrane protein it encodes. Copper is normally pumped into the hepatocyte from the sinusoid through a channel (name redacted), and copper is normally brought to either the vesicle for excretion or the Golgi for ceruloplasmin distribution by a metallochaperone (name redacted). Both still work in Wilson's disease, so copper gets into the cytoplasm. But there is no way to get copper from the cytoplasm into the membrane-bound organelle, whether it be a vesicle or the Golgi. It can't get onto apoceruloplasmin. It can't get into the vesicle destined for the bile canaliculus. So what does copper do? **Copper accumulates in hepatocytes.**

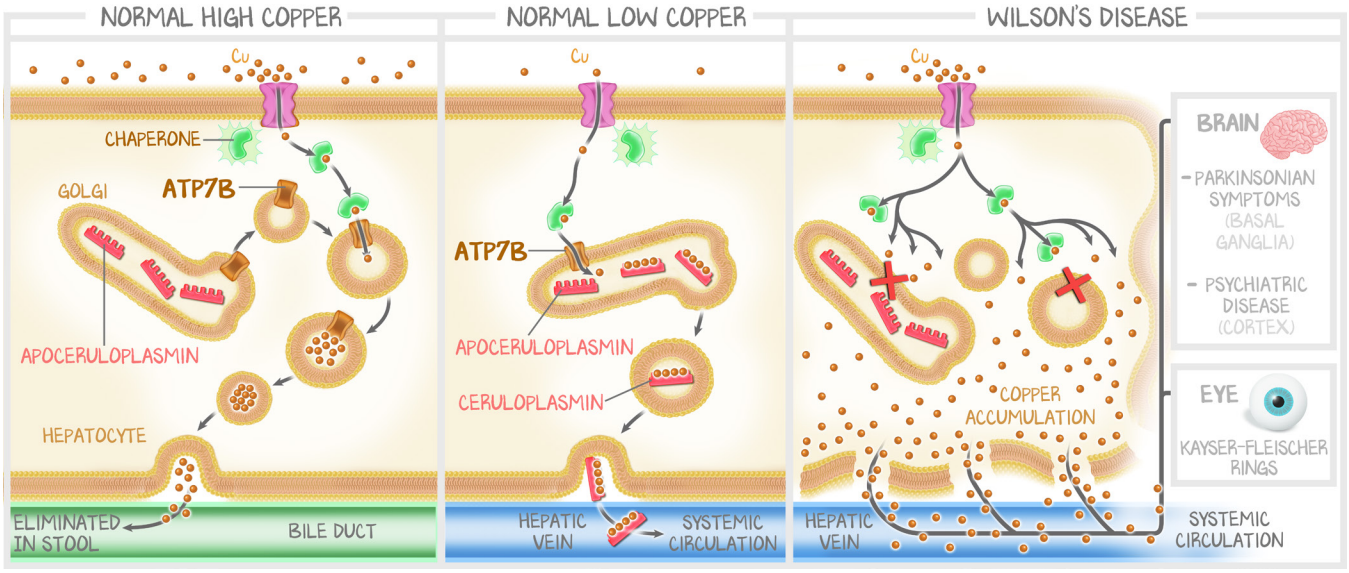

Figure 4.3: Copper Metabolism and Wilson's Disease
In times of high copper, the normal response is to pump copper into a vesicle destined for the bile duct. In times of low copper, the normal response is to pump copper into the Golgi, where apoceruloplasmin is, and then send a vesicle to fuse and release copper as ceruloplasmin. In Wilson's, it matters not whether copper is high or low as the same protein, ATP7B, is broken. Copper can neither be excreted in bile nor attached to apoceruloplasmin. Free copper kills the hepatocyte, then circulates through the bloodstream, only to deposit in tissues. Copper deposits in the basal ganglia causing Parkinsonian symptoms and in the cerebral cortex causing psychiatric issues. Copper deposits in the eye, causing the Kayser-Fleischer rings.

Copper accumulation in the cytoplasm is hepatotoxic and causes hepatocyte necrosis. Necrosis results in acute inflammation—neutrophils, macrophages, fibroblasts. The histology is indicative of hepatocyte toxicity—the same steatosis, Mallory-Denk bodies, and balloon degeneration—of the **pericentral** (zone 3) regions. The biopsy cannot reliably rule in or out Wilson's disease on light microscopy. Instead, it is **the copper content** that makes the diagnosis.

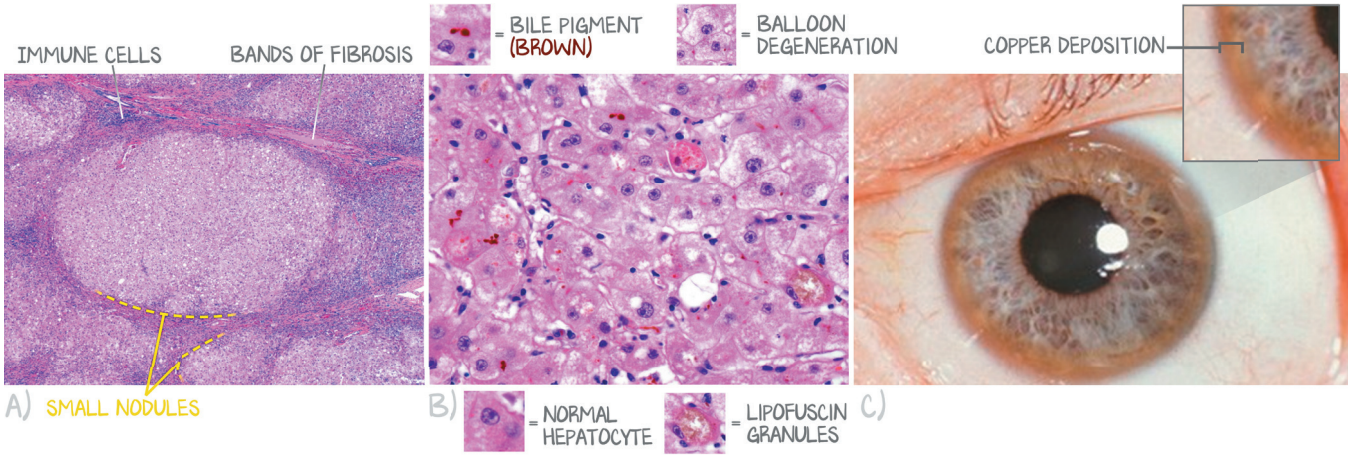

Figure 4.4: Wilson's Disease
Kayser-Fleischer ring: copper deposition in Descemet's membrane of the cornea. These rings can be either dark brown, golden, or reddish-green. They are 1–3-mm wide and appear at the corneal limbus. With rare exceptions, they are diagnostic of inherited hepatolenticular degeneration—Wilson's disease. The following two histology slides show a low-power example and then a high-power example of cirrhosis caused by Wilson's disease. The nodules of hepatocytes are cut off from eachother by bands of fibrosis. The central vein in the top right of the low-power image demonstrates that this is periportal fibrosis. The high-power view shows the attempts of hepatocyte regeneration within the fibrosis, with healthy-appearing hepatocyte flanking the edges of the shot.

Ongoing necrosis yields repeated acute inflammation, which leads to cirrhosis. Macrophages (ongoing inflammation) cleaning up the necrotic hepatocytes induce stellate cells to become fibroblasts that lay down collagen (fibrosis, cirrhosis). Copper spilling into the bloodstream means copper plasma levels increase. But it isn't the copper-bound-to-ceruloplasmin like normal; it's just the element floating around in the blood. This is bad. This causes **copper deposition** in the eyes and brain (and everywhere else, but the disease presents as a liver and neurological problem). Deposition in the **brain** causes Parkinsonian symptoms (basal ganglia) and psychiatric disease (cortex). Deposition into the **eye** causes Kayser-Fleischer rings due to copper deposition into **Descemet's membrane**. On a licensing exam, if there is a liver question with a picture of an eye, the answer is Wilson's.

The diagnosis of Wilson's disease is made definitively by a liver **biopsy** showing **increased hepatic copper content**. It should be considered in anyone showing cirrhotic changes under 30 years old. Normally 10% of the copper absorbed is eliminated through the kidney. In Wilson's disease, the kidney is responsible for all copper elimination. The **screening test** is **increased urinary excretion of copper**. If elevated, a **serum ceruloplasmin** level will be low, as apoceruloplasmin never meets copper to form ceruloplasmin. **Serum copper levels are of no help** because they vary so wildly throughout the disease. Urine copper levels, serum ceruloplasmin levels, and hepatocyte copper levels are the only useful tests.

Early recognition and long-term **copper chelation therapy** (D-penicillamine) or **zinc-based** therapy (blocking copper absorption) can delay the progression of the disease. **Transplant is curative.** The new hepatocytes will not have the genetic defect inherent to this diseased liver.

The overwhelming majority of patients are compound heterozygotes containing different mutations on each *ATP7B* allele. The overall frequency of mutated alleles is 1 in 100, whereas the prevalence of the disease is approximately 1 in 50,000 (approximately 8,000 patients in the United States have the disease). The disease state is STUPID rare, but because it is the only disease of copper metabolism that matters, you are likely to see it on licensing exams.

Hemochromatosis

Hemochromatosis is the disease of iron overload. When that iron overload is caused by an **inherited defect in iron metabolism genes**, it is called **primary hemochromatosis**. If that iron overload is caused by anything else, such as frequent blood transfusions in the major form of β-thalassemia or sickle cell disease (which are inheritable disorders but not of iron metabolism), it is called secondary hemochromatosis. This discussion is on primary hemochromatosis only. Iron regulation and metabolism are discussed in Hematology/Oncology.

Because there is no regulation of iron excretion from the body, the total body content of iron must be regulated by intestinal absorption. **Only iron-in is regulated.** For all intents and purposes, there are **no reliable means of excreting iron** (except bleeding). Enterocytes absorb iron with apical iron transporters and secrete iron into the portal blood with basolateral iron transporters. The **liver** secretes the molecule **hepcidin**. Hepcidin binds to the basal iron transporter on enterocytes, preventing iron from going through the basal domain into the blood. The apical absorption protein is not regulated. This forces the enterocytes to hold on to any iron they absorb. They eventually slough off into the gut when they die, taking their iron with them. Without hepcidin, the enterocytes not only absorb iron but also secrete excess iron into the blood. The normal recommended daily allowance of elemental iron is 10 mg for men and 15 mg for women. Only about 10% of daily ingested iron is absorbed. The normal iron body stores range between 2 g and 6 g. With a **defective *HFE* gene**, the gene that codes for hepcidin, **0.5–1 g extra accumulates every year.** The disease becomes **evident at 20 g** of iron stores and is **florid at 50 g**. That means that although the process is going on all the time, the disease presents itself in middle age, taking decades to accumulate sufficient excess iron to cause disease.

Cells store excess iron as **hemosiderin**. Primary hemochromatosis results in the deposition of hemosiderin in the **liver** (leading to cirrhosis), **pancreas** (leading to diabetes), **myocardium** (leading to diastolic heart failure), **pituitary gland** (causing hypogonadism and varying degrees of endocrinopathies), **skin** (causing hyperpigmentation due to the upregulation of melanocyte activity), and **joints** (causing arthritis). Hemosiderin is brown. On gross sections of the liver, there will be micronodular cirrhosis, and the liver will appear **dense** and **chocolate brown**. On histology, **periportal hepatocytes** (zone 1 first, then progressing towards the central vein) stain positive for hemosiderin with **Prussian blue**. Both lipofuscin (*lie-poh-FEW-shin*) and hemosiderin are brown on a regular H&E stain. Only iron, hemosiderin, turns blue on Prussian blue stain. As more iron overload occurs, there is progressive involvement of the rest of the lobule.

The classic presentation is **bronzed diabetes**—micronodular cirrhosis, diabetes mellitus, and abnormal skin pigmentation. Iron accumulation in hereditary forms is lifelong, but the injury caused by excessive iron presents itself later in life, and only after iron levels become toxic. Patients present in their **40s or 50s**. A significant cause of death is hepatocellular carcinoma; the risk is 200-fold greater than that in the general population. There is no way to get iron out of the body. The exception to this is hemorrhage. Women with menstrual cycles have a regular means of eliminating iron. Every other human does not. The greatest demand for iron is pregnancy, something only women experience. Therefore, women with the mutation either do not become symptomatic or, if they do, present much later in life compared to males (no menses and no pregnancy).

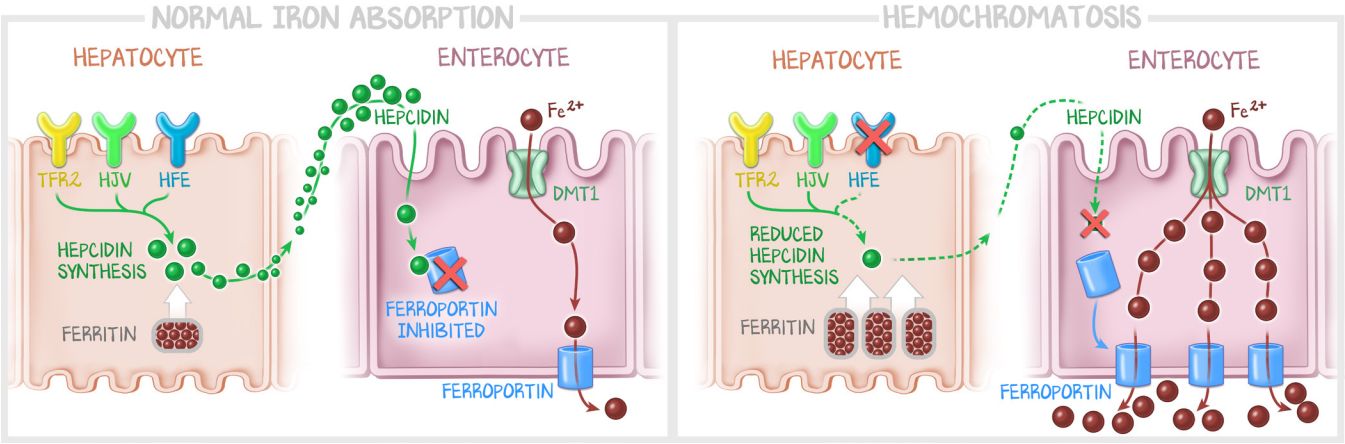

Figure 4.5: Iron Metabolism and Hemochromatosis
With normal *HFE* genes, hepcidin is released in response to excess hepatic iron, inhibiting ferroportin. With *HFE* gene mutations and less hepcidin, even though there is copious hepatic (and total body) iron, ferroportin remains disinhibited, and excess iron accumulates.

Fortunately, hemochromatosis can be diagnosed long before irreversible tissue damage has occurred. Treatment with regular **phlebotomy** steadily depletes tissue iron stores. In addition, iron chelation can be used with deferoxamine ("*de-ferox-a-me*"). With treatment, life expectancy is normal. Screening involves the demonstration of very high levels of serum iron and **very high levels of ferritin**. A very high level of iron likewise saturates transferrin, so the transferrin saturation will also be high. A **liver biopsy** may be indicated; it was formerly the only way to inform the diagnosis. With the ability to screen for specific gene mutations, biopsy and iron content of the biopsy is no longer necessary. Hemochromatosis is one of the few diseases that will get the ferritin into the 1000s.

If a patient develops cirrhosis and is transplanted, because the genetic defect is of hepatocyte production of hepcidin, the disease cannot recur. The enterocytes may do the absorbing, but the *HFE* gene, and thus the protein of enterocyte regulation (hepcidin), is a protein made by hepatocytes. With a new liver without the *HFE* mutation, hepcidin is made normally. With phlebotomy, few patients progress to cirrhosis or need a transplant.

α-1 Antitrypsin (ATA1) Deficiency

ATA1 is a **protease inhibitor**, particularly of the neutrophil elastase. ATA1 deficiency causes problems in the **liver** due to **misfolded protein accumulation** and results in cirrhosis. **Hepatocytes make ATA1**. Because the protein is misfolded in the diseased form, hepatocytes won't let the protein out of the endoplasmic reticulum, and so it accumulates. Accumulation of anything in a cell is never good. ATA1 deficiency also causes problems in the **lung**. Neutrophils secrete elastase to clear out invaders. Cigarette smoking activates neutrophils, releasing elastase. That elastase also happens to chew up the septa of alveoli; it degrades elastin. Normally, there is ATA1 around to balance that elastase activity. In the diseased state, ATA1 deficiency permits elastase to go unbalanced and unchecked, leading to early emphysema. ATA1 deficiency, the classic syndrome, is therefore **early emphysema and cirrhosis**.

There are two allele types of import. M is normal. Z is broken. The protease inhibitor alleles are described as PiM and PiZ. We are massively simplifying this disease to eliminate confusion. It IS different from the way we communicate most genetic diseases, but we've pared it down to simple Mendelian genetics. PiMM is wildtype. PiMZ is a heterozygote. PiZZ is the diseased allele combination: two alleles, both with loss-of-function mutations. This is an **autosomal recessive** disorder. In patients with the PiZZ genotype, less than 10% of ATA1 is produced. SOME ATA1 gets into the

bloodstream, so there isn't a total deficiency. But that means more than 90% ends up in hepatocytes, activating inflammation when they die and apoptosis when the hepatocytes recognize what's happening.

A diagnosis can be made on **liver biopsy** showing **PAS-positive hepatocytes** or with **genetic testing** for the protease inhibitor allele.

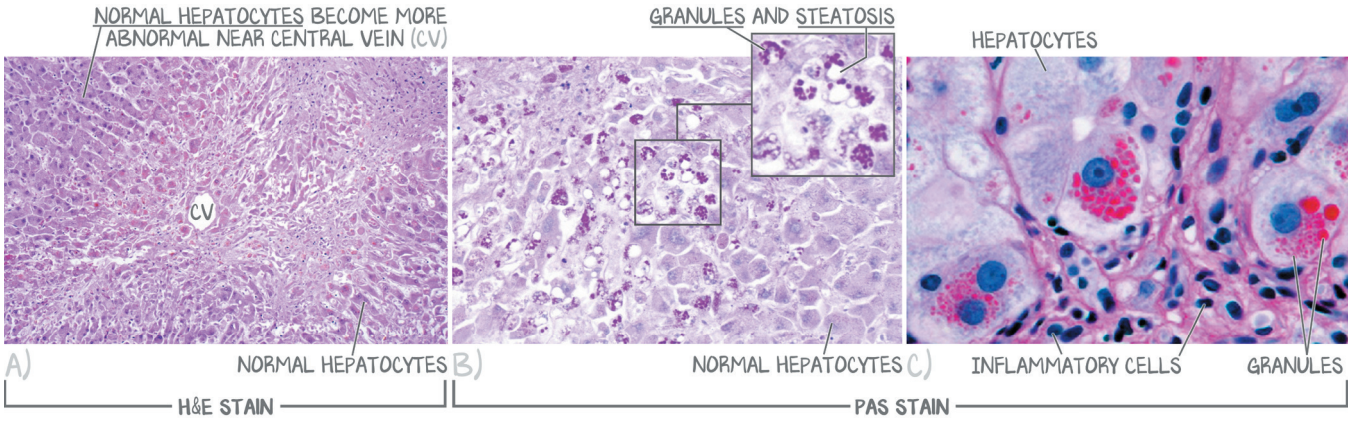

Figure 4.6: α-1 Antitrypsin Deficiency
(a) The most characteristic histological finding in α-1 antitrypsin deficiency is the accumulation of globular eosinophilic cytoplasmic inclusions within periportal hepatocytes. These inclusions are periodic acid-Schiff (PAS)-positive and diastase-resistant and appear as magenta-colored granules in the cytoplasm. The inclusions vary in size and increase in number as the patient ages. Note the uneven distribution of granules in this image. (b) High-powered view of hepatocytes with clear cytoplasm, stained to reveal the brightly eosinophilic granules. These are PAS-D+ globules. The globules are 1–10 microns in diameter. (c) The biggest globules from panel b can be seen here, stained with H&E.

Because the hepatocyte carries the faulty gene, transplant is curative. Smoking cessation can spare the patient from emphysema.

Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD was previously non-alcoholic steatohepatitis (NASH), and now both are used interchangeably. NAFLD has histology that **looks like alcoholic** liver disease and **progresses like alcoholic** liver disease but in someone engaging in **no alcohol consumption**. The predominant feature of NAFLD is **pericentral hepatocytes** filled with fat droplets (steatosis, just like alcoholic liver disease). The pericentral hepatocytes are involved in fatty acid synthesis and the detoxification of drugs, such as alcohol. It makes sense that if fat is going to accumulate somewhere in the liver, it would be in these zone 3 hepatocytes. The same discussion we had in alcoholic liver disease. The name steatohepatitis has been replaced by NAFLD because, like in alcoholic liver disease, the signs of acute inflammation that would warrant the name hepatocyte-itis are not always present, although steatosis and steatofibrosis are.

The proposed mechanism is that **insulin resistance** and increased calories result in the hepatocytes doing what they do—making fatty acids and assembling them as triglycerides, making fat. Fat-laden cells are highly sensitive to lipid peroxidation products generated by oxidative stress, which can damage mitochondrial and plasma membranes, causing apoptosis. The way this works practically is that someone gets cirrhosis. They get a biopsy to confirm it because they are going on the transplant list, and what is found is pericentral steatofibrosis. Their alcohol testing is negative. They are given the diagnosis of NAFLD. Non-alcoholic fatty liver disease may show all the changes associated with alcoholic liver disease: steatosis, steatohepatitis, and steatofibrosis (e.g., hepatocyte ballooning, Mallory-Denk bodies, and neutrophilic infiltration).

There are likely causes of NAFLD that we have not yet elucidated, NAFLD being the histologic phenotype rather than a specific diagnosis. Because thin patients without metabolic syndrome also get NAFLD, metabolic syndrome cannot be the sole cause. For this stage of your training, **NAFLD is the liver disease of insulin resistance** and is associated with metabolic syndrome: obesity, type 2 diabetes mellitus or other impairments of insulin responsiveness, dyslipidemia, and hypertension.

CAUSE	NOTES
Viral	Cirrhosis and . . . needle drugs (Hep C), Asia vertical transmission (Hep B)
Wilson's Disease	Cirrhosis and . . . Kayser-Fleischer rings, Parkinson's, and psychiatric Presents in the 30s with liver failure *ATP7B* gene mutation, impaired copper transport into vesicles Lost ability to form ceruloplasmin (serum ceruloplasmin levels low) Lost ability to form copper vesicles for biliary elimination (urine Cu increases) Confirm with biopsy Treat with penicillamine, transplant
Hemochromatosis	Cirrhosis and . . . diabetes, heart failure, dark skin Presents in the 50s with liver failure and "bronze diabetes" *HFE* gene mutation, hepcidin loss, disinhibited iron absorption at enterocytes Screen with high ferritin, liver biopsy confirmatory Prussian blue stains iron stores with normal architecture Chocolate liver Treat with phlebotomy and iron chelators (deferoxamine)
α-1 Antitrypsin Deficiency	Cirrhosis and . . . COPD PiM normal, PiZ abnormal, PiZZ has 10% α-1 antitrypsin PAS-positive macrophages in hepatocytes
PSC	Cirrhosis and . . . ulcerative colitis, biliary cirrhosis pattern
PBC	Cirrhosis and . . . intrahepatic fibrosis, biliary cirrhosis pattern
Alcohol	Cirrhosis and . . . alcohol consumption Steatosis from chronic alcohol = pericentral hepatocyte fat accumulation Steatohepatitis from acute alcohol = neutrophils, 20% mortality Steatofibrosis from chronic alcohol and hepatitis = pericentral fibrosis Affects zone 3
NAFLD	Cirrhosis and . . . metabolic syndrome Follows alcoholic liver disease histologically Steatosis (fat in cells), steatohepatitis (fat in cells surrounded by inflammatory cells), then ultimately steatofibrosis (fat in cells surrounded by scar)

Table 4.1: Summary of Metabolic Liver Disease

Citations

Figures 4.2: Courtesy of WebPathology.com.

Figure 4.4a: by Herbert L. Fred & Hendrik A. van Dijk, licensed under CC-BY-SA-3.0.

Figures 4.4b, 4.4c, 4.6a, 4.6b, 4.6c: Courtesy of WebPathology.